IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Siegfried ANSORGE et al.	Examiner: SIMMONS, CHRIS E
Serial No.: 10/584,072	Group Art Unit: 1612
Filed: APRIL 3, 2007	Confirmation No.: 6887

Title: **USE OF AT LEAST ONE EFFECTOR OF GLUTATHIONE METABOLISM TOGETHER WITH ALPHA-LIPOIC ACID FOR THE TREATMENT OF CHRONICALLY OBSTRUCTIVE LUNG DISEASES**

BRIEF ON APPEAL UNDER 37 C.F.R. § 41.37

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Sir:

Further to the Notice of Appeal filed September 11, 2009 and the pre-appeal brief (PAB) conference request filed concurrently therewith, attached is Appellants' Brief on Appeal, pursuant to 37 CFR §41.20(b)(2). An authorization to charge the requisite fee set forth under 37 CFR §41.20(b)(2) is also enclosed herewith.

This is an appeal from the decision of the Examiner finally rejecting claims 1-3, 5-8 and 10-15 of the above-identified application under 35 USC §103(a). The final rejection was mailed on June 11, 2009. On September 11, 2009, Applicants filed the PAB request and a decision thereto was mailed on January 5, 2010. Insofar as this paper is being filed within one month from the mailing date of the decision, it is considered timely. See item 2 at page 2 of the panel decision.

(I) REAL PARTY IN INTEREST

ESPARMA GmbH of Osterweddingen, GERMANY is the Assignee of Record of the entire right, title, and interest in and to the above-identified application, as recorded in the U.S. Patent and Trademark Office on April 3, 2007, at Reel/Frame 019106/0469.

(II) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or

interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(III) STATUS OF THE CLAIMS

Claims rejected:	Claims 1-3, 5-8 and 10-15.
Claims allowed:	(None).
Claims cancelled:	Claims 4 and 9.
Claims withdrawn:	(None).
Claims on Appeal:	Claims 1-3, 5-8 and 10-15. (Copy of claims on appeal in the attached Appendix).

(IV) STATUS OF AMENDMENTS

In the Claims Appendix section of this brief, the amendments presented with the non-final Reply of March 24, 2009 (to the Office Action of December 24, 2008) are entered and are reflected.

(V) SUMMARY OF CLAIMED SUBJECT MATTER

One aspect of Appellants' invention (independent claim 1) is directed to a method for the cytoprotective treatment of chronically obstructive lung, comprising administering to a subject in need thereof an effective dose of a combination consisting of (a) silibinin or a salt thereof and (b) α-lipoic acid or a salt thereof, and an additive which is an aqueous solvent, a stabilizer, a suspending agent, a dispersing agent or a wetting agent for each of silibinin (or its salt) and α-lipoic acid (or its salt). The combination is administered by inhalation in a simultaneous, separate, or timed manner. See, for example, the disclosure contained in the paragraphs bridging page 4, line 13 to page 7, line 3 of the originally-filed specification and the disclosure contained in the Examples. Claims 2, 3, 6-8 and 10-15 are directly or indirectly dependent on the aforementioned independent claim 1, and recite additional aspects of the instantly claimed method. For example, claim 2 is directed to methods for the cytoprotective treatment of chronically obstructive lung in a human patient comprising administering silibinin or a salt thereof and α-lipoic acid or a salt thereof, wherein the concentration of the α-lipoic acid or a salt thereof is between 30 and 1800 mg/d. See, for example, page 5, lines 14–18 of the originally-filed specification. Claim 3 is directed to methods for the cytoprotective treatment of chronically obstructive lung in a human patient comprising administering silibinin or a salt thereof and α-lipoic acid or a salt thereof, wherein the dose of the silibinin or a salt thereof is between 20 and 1600 mg/d. See, for example, page 6, lines 9–13 of the

originally-filed specification. Claim 6 recites that each of silibinin (or its salt) and α-lipoic acid (or its salt) is presented in the form of an aerosol. Support for the claim can be found in, for example, page 6, lines 23–29 of the originally-filed specifcation. Claims 7 and 8 recite that the silibinin or a salt thereof and the α-lipoic acid or a salt thereof are presented in a single formulation and separate formulation, respectively. See, for example, 1st paragraph at page 7 of the originally-filed specification. Claims 10 and 11, which depend on aforementioned claims 7 and 8, are directed to the use of silibinin and α-lipoic acid (in their native form). Support for the claim can be found in, for example, the disclosure in Example 2. Claim 12 recites that the molecules of the instant invention, in their native form (i.e., silibinin and α-lipoic acid) are presented with an additive which is an aqueous solvent, a stabilizer, a suspending agent, a dispersing agent or a wetting agent. Support for the claim can be found in, for example, original claim 8 and paragraph [0024] of the published application. Claims 13–15, which depend on instant claim 1, recite dosage ranges for each silibilin and lipoic acid that are to be administered to the subject having chronically obstructed lung. Support for these claims can be found in, for example, the disclosure bridging page 5, line 10 to page 6, line 13 of the originally-filed specification.

Another aspect of Applicants' invention (claim 5) is directed to the cytoprotective treatment of chronically obstructive lung, comprising administering to a subject in need thereof an effective dose of a combination consisting of (a) silibinin or a salt thereof, optionally together with an additive which is an aqueous solvent, a stabilizer, a suspending agent, a dispersing agent or a wetting agent; and (b) α-lipoic acid or a salt thereof, optionally together with an additive which is an aqueous solvent, a stabilizer, a suspending agent, a dispersing agent or a wetting agent; wherein each of silibinin (or its salt) and α-lipoic acid (or its salt) are administered to the subject by inhalation in a simultaneous, separate, or timed manner. See, for example, page 6, lines 23–29 of the originally-filed specifcation for support.

(VI) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Appellants request a review of the following remaining grounds of rejection. For each ground, any separate grouping of the claims subject to that rejection is indicated. As per the requirements under 37 CFR §1.113(a), objections of formal nature are not being appealed.

(1) The rejection of claims 1-3, 5-8 and 10-15 under §103(a) as allegedly rendered obvious by Biewenga et al. (*ABB*, 1994), Mira et al. (*Biochem. Pharmacol.*, 1994) further in view of Yeadon (US publication No. 2004-0167153; *hereinafter* the '153 publication).

Grouping of claims

Claims 2, 3, 6–8, and 10–15 stand or fall together with independent claim 1.

Independent claim 5 stands or falls independently from claim 1.

(VII) ARGUMENT

Rejections under §103

Claims 1-3, 5-8 and 10-15 are rejected under §103(a) as allegedly rendered unpatentable by Biewenga et al., Mira et al. further in view of Yeadon et al. This rejection is not supported on the record as a whole and should be reversed.

The Office Action mailed December 24, 2008 alleges that the instantly claimed method(s) are unpatentable over Biewenga et al., Mira et al. further in view of Yeadon. The Office Action mailed June 11, 2009 sustains this rejection. The basis for this rejection is that Biewenga's disclosure on the usefulness of α-lipoic acid against lung emphysema in combination with Mira's disclosure of the use of silibinin as an antioxidant and HOCl scavenger, *prima facie* renders obvious the claims of the instant application. The Office Action cites *In re Kerkhoven* 205 USPQ 1069 (CCPA 1980) to assert that "The combination of compounds for a certain function where the compounds are known to have the function individually is *prima facie* obvious." At the outset, Appellants submit that this statement is incorrect. In *Kerkhoven*, the CAFC held that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose (emphasis added)." In view of the Examiner's misplaced reliance on *In re Kerkhoven*, the *prima facie* obviousness rejection is without merit. Favorable action is earnestly solicited.

Unexpected effects

In applying *Kerkhoven*, the Office Action asserts that "there is no evidence in the record establishing the Appellant's combination of agents is any more effective or in any way different than any single member of the combination." This statement is incorrect. The instant specification explicitly teaches to a skilled worker that the claimed invention involves much more than mere mixing of the two compounds and that the claimed combination leads to "unexpected results." To this end, the Board is cordially requested to review the disclosure contained in Tables 6 and 7 and the analysis thereof provided in Examples 4 and 5.

For example, in Example 4 of the instant specification, an unexpected effect of a combination of α-lipoic acid and silibilin on the cellular thiol status of alveolar macrophages is disclosed. It is taught therein that "With the addition of the monosubstances α-lipoic acid or

silibinin, no modulation of the cellular thiol expression was to be observed. In contrast, with the combination of α-lipoic acid and silibinin, a clear rise in cellular thiol expression could be demonstrated, starting after 24 hours, which reached a superadditive and significant maximum over the entire test period in the presence of 70 µg/ml silibinin. (emphasis added)." Similarly, in the *ex vivo* phagocytosis assay (e.g., Example 5), it was demonstrated that "the induction of phagocytosis with the combination of α-lipoic acid and silibinin in a concentration of 70 µg/ml was similar [to the one afforded by a combination of α-lipoic and ambroxol]. Here, too, a significant improvement in the capacity for phagocytosis was demonstrated, parallel to a restoration of the thiol status (emphasis added)." Thus it is clear from the experimental evidence disclosed in the instant application that the claimed molecules(s) display unexpected advantages over the totality of the disclosure contained in the cited references. The specification's evidence must be given weight. See *In re Soni*, 54F3d 746, 34USPQ2d1684 (Fed. Cir. 1985).

As evidenced from the Examiner's remarks in the final action mailed June 11, 2009, the evidence of unexpected properties of the claimed combination has not been considered on its merits. The Office Action now alleges that there is no side by side comparison of the closest art. This contention is simply incorrect. Based on the Examiner's rejection, the closest prior art is the combined teachings by Biewenga and Mira, which, at most, disclose the biochemical effects of α-lipoic acid or silibinin administration (i.e., there is no disclosure that the agents can be combined). The Office Action surmises that the agents could be combined. However, such is impermissible hindsight. More importantly, the rationale to combine the two agents is only provided by Applicant's disclosure. To this end, Example 4 of the present specification provides a side-by-side comparison of the agents when used singularly and in combination. In particular, the disclosure therein evaluates the effects of "monosubstances" (i.e., α-lipoic acid or silibinin) *versus* the claimed combination with respect to elevation of intracellular thiol status in COPD cells. The experimental evidence provided therein explicitly teaches that the claimed combination yields an unexpected (e.g., superadditive) effect. Furthermore, the claimed combination's effects on *in vitro* thiol status were found to correlate with the *in vivo* activity (shown in Example 5). Thus, although not required, the experimental evidence clearly establishes unexpected properties of the claimed combination in the *in vitro* as well as *in vivo* setting. It would clearly be disingenuous for the PTO to sustain this rejection in view of the totality of the evidence provided by the present disclosure.

The Examiner further questions the validity of the control experiments (i.e., results of experiments performed with 70 µg of silibinin or 10 µg of lipoic acid). The Examiner's position is that "proper showing of unexpected results would include a comparison to 80 µg of lipoic acid alone

and 80 μg of silibinin alone." This contention is without merit because there is no requirement that the exact same doses of α-lipoic acid and silibilin be used in the comparative assessment. All is required is that the amounts of the respective agents in the combination be identical to that which is used in singularity. Such has been established by the present disclosure. For example, as shown in Table 6, the intracellular thiol concentration in COPD cells at 24 hours was 61.6% ±13.9% of normal cells. When the same COPD cells were treated with 10 μg of α-lipoic acid or 70 μg of silibilin, the intracellular thiol status was essentially unchanged (60.3% ±21% with α-lipoic acid and 56.1% ±12.4% with silibilin). However, with a combination of 10 μg α-lipoic acid and 70 μg of silibilin, the intracellular thiol status was elevated up to and beyond normal levels (102.5% ± 22.6%). Similar observations were reported in the *in vivo* phagocytosis assay, the results of which are provided in Table 7. As such, the PTO's contentions are scientifically baseless.

The Office Action mailed June 11, 2009 further alleges that "the claims are not commensurate in scope to any example in Tables 6 or 7." This contention is respectfully traversed. Insofar as the objective indicia of unobviousness for the claimed combination has been established by the way of experimental evidence, and the Examiner has failed to provide any reasons as to why one of ordinary skill would doubt that doses that are different from the exemplified doses would cease to yield the demonstrated pharmacological effects, the PTO's contentions are without merit. The data provided by the present specification are more than adequate. See *In re Saunders*, 444 F.2d 599, 170 USPQ 213 (CCPA 1971).

No *prima facie* case

Appellant respectfully submits that the PTO has not established that the claimed methods are rendered *prima facie* obvious by the disclosure in the aforementioned references. To this end, the decision in *Kerkhoven* was made with respect to spray-dried detergent compositions comprising two detergents, one anionic and the other nonionic detergent materials, whereas the agents used here have different biological targets and, as such, effects. Contrary to the PTO's assertion, the compounds of each reference are not taught for the same specific purpose. Clearly, the pharmacology of the two agents is different, as are the disclosed uses. The cited teachings of Biewenga and Mira, even at the broadest interpretation, do not teach or suggest the combined use of the two molecules in the manner recited in the instant claims. Withdrawal of the rejection is respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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(VIII) CLAIMS APPENDIX

Claim 1. A method for the cytoprotective treatment of chronically obstructive lung, comprising administering to a subject in need thereof an effective dose of a combination consisting of
(a) silibinin or a salt thereof
and
(b) α-lipoic acid or a salt thereof,
and an additive which is an aqueous solvent, a stabilizer, a suspending agent, a dispersing agent or a wetting agent for each (a) and (b),
wherein each of (a) and (b) are administered to said subject by inhalation in a simultaneous, separate, or timed manner.

Claim 2. The method according to claim 1, wherein said subject is a human patient and the dose of said α-lipoic acid or a salt thereof is between 30 and 1800 mg/d.

Claim 3. The method according to Claim 1, wherein said subject is a human patient and the dose of said silibinin or a salt thereof is between 20 and 1600 mg/d.

Claim 5. A method for the cytoprotective treatment of chronically obstructive lung, comprising administering to a subject in need thereof an effective dose of a combination consisting of
(a) silibinin or a salt thereof, optionally together with an additive which is an aqueous solvent, a stabilizer, a suspending agent, a dispersing agent or a wetting agent; and
(b) α-lipoic acid or a salt thereof, optionally together with an additive which is an aqueous solvent, a stabilizer, a suspending agent, a dispersing agent or a wetting agent; wherein each of (a) and (b) are administered to said subject by inhalation in a simultaneous, separate, or timed manner.

Claim 6. The method according to Claim 1, wherein each of (a) and (b) is presented in the form of an aerosol.

Claim 7. The method according to Claim 1, wherein silibinin or a salt thereof and the α-lipoic acid or a salt thereof are presented in a single formulation.

Claim 8. The method according to Claim 1, wherein silibinin or a salt thereof and the α-lipoic acid or a salt thereof are presented in separate formulations.

Claim 10. The method according to Claim 7, wherein the silibinin and the α-lipoic acid are presented in a single formulation.

Claim 11. The method according to Claim 8, wherein the silibinin and the α-lipoic acid are presented in separate formulations.

Claim 12. The method according to Claim 1, wherein the combination consists of
(a) silibinin and
(b) α-lipoic acid,
and an additive which is an aqueous solvent, a stabilizer, a suspending agent, a dispersing agent or a wetting agent for each (a) and (b).

Claim 13. The method according to claim 2, wherein the dose of α-lipoic acid or a salt thereof is between 200 and 600 mg/d.

Claim 14. The method according to claim 3, wherein the dose of silibinin or a salt thereof is between 300 and 800 mg/d.

Claim 15. The method according to Claim 1, wherein said subject is a human patient and the dose of said silibinin or a salt thereof is between 20 and 1600 mg/d and the dose of said α-lipoic acid or a salt thereof is between 30 and 1800 mg/d.

(IX) EVIDENCE APPENDIX

Appendix of evidence submitted pursuant to §§ 1.130, 1.131, or 1.132 of this title or of any other evidence entered by the Examiner and relied upon by appellant in the appeal, along with a statement setting forth where in the record that evidence was entered in the record by the Examiner. Copies of the evidentiary documents are attached.

Reference/Exhibits	Entered in the Record
1. Keller et al., "Method of treatment of glutathione deficient mammals" US patent No. 6,262,019.	Cited by the Examiner in the Office Action mailed October 2, 2007. A copy of the reference was provided and entered on the record. Reliance thereon maintained in the final Office Action mailed May 29, 2008. Reliance thereon withdrawn in the Office Action mailed December 24, 2008.
2. Engelen et al., "Altered Glutamate Metabolism Is Associated with Reduced Muscle Glutathione Levels in Patients with Emphysema." *Am. J. Respir. Crit. Care Med.*, Volume 161, Number 1, January 2000, 98-103.	Cited by the Examiner in the Office Action mailed October 2, 2007. A copy of the reference was provided and entered on the record. Reliance thereon withdrawn in the Office Action mailed May 29, 2008.
3. Smit et al., "Method of increasing the presence of glutathione in cells." US patent No. 6,495,170.	Cited by the Examiner in the Office Action mailed October 2, 2007. A copy of the reference was provided and entered on the record. Reliance thereon withdrawn in the Office Action mailed May 29, 2008.
4. Valenzuela et al., "Selectivity of silymarin on the increase of the glutathione content in different tissues of the rat." *Planta Med.*, 1989 Oct;55(5):420-2 (ABSTRACT).	Cited by the Examiner in the Office Action mailed October 2, 2007. A copy of the reference was provided and entered on the record. Reliance thereon withdrawn in the Office Action mailed May 29, 2008.
5. Bisgaard et al. "Drug delivery to the lung." *Informa Healthcare*, 1st Ed. (2002) ISBN: 0824705416.	Cited by the Examiner in the Office Action mailed May 29, 2008. A copy of the reference was provided and entered on the record. Reliance thereon withdrawn in the Office Action mailed May 29, 2008.
6. Biewenga et al. "Lipoic acid favors thiolsulfinate formation after hypochlorous acid scavenging: a study with lipoic acid derivatives." *Arch Biochem Biophys.*, 1994 Jul;312(1):114-20.	Cited by the Examiner in the Office Action mailed December 24, 2008. A copy of the reference was provided and entered on the record. Reliance thereon maintained in the final Office Action mailed June 8, 2009.

(IX) EVIDENCE APPENDIX…

7. Mira et al. "Scavenging of reactive oxygen species by silibinin dihemisuccinate." *Biochem Pharmacol*, 1994 Aug 17;48(4):753-9.	Cited by the Examiner in the Office Action mailed December 24, 2008. A copy of the reference was provided and entered on the record. Reliance thereon maintained in the final Office Action mailed June 8, 2009.
8. Yeadon et al. "Pharmaceutical combination." US patent application pub. No. 2004-0167153.	Cited by the Examiner in the Office Action mailed December 24, 2008. A copy of the reference was provided and entered on the record. Reliance thereon maintained in the final Office Action mailed June 8, 2009.

(X) RELATED PROCEEDINGS APPENDIX

(None)